LEWIS-ACID CATALYSIS OF A DIELS-ALDER REACTION IN WATER

Otto, S.; Engberts, J.B.F.N.

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Lewis-Acid Catalysis of a Diels-Alder Reaction in Water

Sijbren Otto and Jan B.F.N. Engberts*

Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

Abstract: The reaction between the diene **1** and cyclopentadiene (**2**) is efficiently catalysed by small amounts of Lewis acids (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}). The reaction in an aqueous solution containing 0.010 M $Cu(NO_3)_2$ is 250.000 times faster than that in acetonitrile. This huge acceleration is the result of a combination of the accelerative solvent effect of water and catalysis by Cu^{2+} as the Lewis acid.

Diels-Alder (DA) reactions are normally (nearly) synchronous and concerted processes. The reactions are traditionally characterized by modest solvent effects[1], in accordance with small changes in charge on going from the reactants to the activated complex. Breslow's observation[2] in 1980 that DA reactions can undergo large accelerations in water was at that time rather unexpected.

The DA reaction is not the only bimolecular transformation which shows a remarkable acceleration on going from organic solvents to water. Also rate enhancements of, inter alia, the Claisen rearrangement, the aldol condensation and the benzoin condensation in water have been reported[3].

Since Breslow's first report there has been an extensive discussion about the origin of the acceleration in aqueous media. The different proposals have been briefly reviewed in ref. 4c. In previous studies[4] we have concluded that there are two major factors responsible for the fast reactions in water. The first involves the notion that enforced hydrophobic interactions[5] destabilize the initial state relative to the activated complex, thereby increasing the rate of the reaction in water. Secondly, hydrogen bonding of water to the activating group(s) stabilizes the polarized activated complex, leading to a significant rate enhancement. Recent computer simulations by Jorgensen et al[6] strongly support these suggestions.

The beneficial effect of water as a solvent has also been exploited in organic synthesis[3b,7].

In view of the origin of the marked solvent effect of water, we wondered whether the rate of the DA reaction in water could be even further enhanced by Lewis-acid catalysis. To our knowledge there are no previous examples of Lewis-acid catalysis of DA reactions in water[8], despite the fact that this type of catalysis is well documented for nonaqueous solvents[9]. At the outset of our studies, several points had to be considered.

First of all catalysis requires complexation of the catalyst to one of the reactants. In order to achieve

this, both substrate and catalyst need to be partly dehydrated. The unfavorable change in Gibbs energy accompanying this dehydration process has to be more than compensated for by a particularly favorable Gibbs energy of complexation. It was anticipated that bidentate complexation should in principle be able to fullfill this requirement.

Secondly, once the complex has been formed, it should undergo a DA reaction exclusively and no side reactions should be induced by substrate polarization, such as Michael addition of water.

Finally, after the DA reaction has taken place, the complex with the Lewis acid should dissociate in order to allow a favorable turn-over number.

Based on these considerations, we envisaged that the DA reaction of 3-(p-nitrophenyl)-1-(2-pyridyl)-2-propene-1-one (**1**)[10] with cyclopentadiene (**2**) might be promising (see Figure 1). Since **1** has a strong UV absorbance at 310-330 nm, reaction rates could easily be determined by UV spectroscopic techniques. Kinetic data and Gibbs energies of activation of the reaction of **1** with **2** are summarized in Table 1.

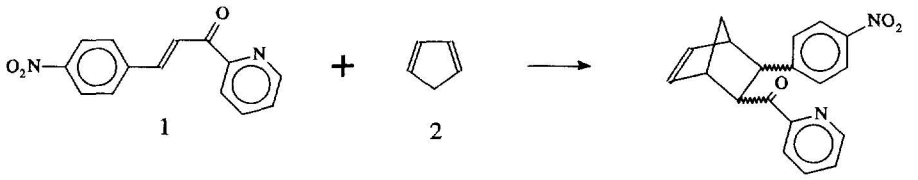

Fig. 1.

The reaction of **1** with **2** in ethanol and acetonitrile is very slow. As expected, water enhances the rate of the reaction significantly. Interestingly, introduction of small amounts of Lewis acids, particularly Cu^{2+}, leads to even faster reactions. We suggest that these Lewis-acid catalyzed reactions proceed via an activated complex schematically shown in Figure 2. Compared to acetonitrile, the reaction in 0.010 M $Cu(NO_3)_2$ in water is about 250 000 times faster !

Correlation of the second-order rate constants with the concentration of $Cu(NO_3)_2$ is nonlinear (Figure 3). At higher concentrations the rate of the reaction clearly levels off, most likely because at these concentrations **1** becomes completely bound to the copper catalyst.

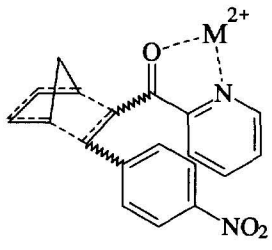

Fig. 2.

Comparison of the rates in solutions of 0.010 M $Cu(NO_3)_2$ in ethanol and in water makes it clear that the accelerative solvent effect of water is still present in the Lewis-acid catalysed reaction.

The 19-fold increase in the rate in 0.010 M HCl compared to pure water provides evidence that the reaction is also subject to Brønsted-

acid catalysis.

Preliminary results show that the reaction of **1** with **2** is also catalysed by other Lewis-acids such as $Co(NO_3)_2$, $Ni(NO_3)_2$, and $Zn(NO_3)_2$ although these Lewis acids are less efficient than $Cu(NO_3)_2$. The relative order $Co^{2+} < Ni^{2+} < Cu^{2+} >> Zn^{2+}$ is in accordance with the trends in stability constants reported for complexes of these metal ions with various chelating agents[11].

To our knowledge the present results are the first examples of Lewis-acid catalysis of a DA reaction in aqueous solution. Further detailed kinetic studies are in progress.

Table 1. Second-order rate constants and Gibbs energies of activation for the reaction of 1 with 2 in different media at 25 °C

Reaction medium	2^{nd} order rate constant ($M^{-1}s^{-1}$)	Gibbs energy of activation (kJ mol^{-1})
acetonitrile	$1.32\ 10^{-5}$	101
ethanol	$3.83\ 10^{-5}$	98.2
water	$4.02\ 10^{-3}$	86.7
0.010 M $Cu(NO_3)_2$ in water	3.25	70.1
0.010 M $Cu(NO_3)_2$ in ethanol	0.769	73.6
0.010 M HCl in water	$7.62\ 10^{-2}$	79.4

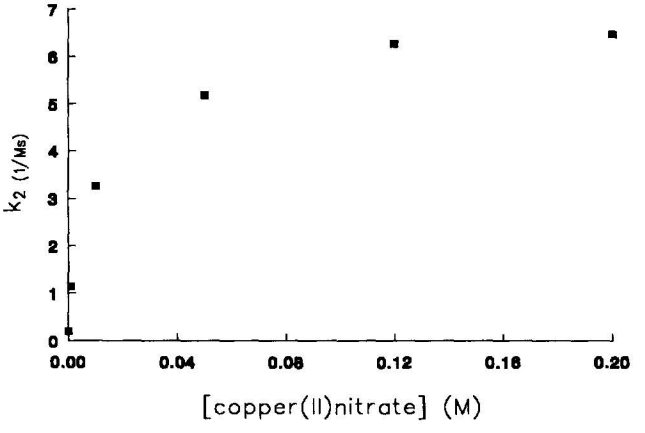

Fig. 3. Second-order rate constants for the DA reaction of **1** with **2** in aqueous solution as a function of the concentration copper(II)nitrate

Acknowledgement

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References and Notes

1. (a) Sauer, J.; Sustmann, R. *Angew.Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Cambridge, 1990.

2. Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7817.

3. For recent reviews see: (a) Li, C.; *Chem. Rev.* **1993**, *93*, 2023. (b) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis*, **1994**, 741.

4. (a) Blokzijl, W.; Blandamer, M.J.; Engberts, J.B.F.N. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J.B.F.N. *J. Am. Chem. Soc.* **1992**, *114*, 5440. (c) Otto, S.; Blokzijl, W.; Engberts, J.B.F.N. *J. Org. Chem.* **1994**, 59, 5372. (d) Wijnen, J.W.; Engberts, J.B.F.N.; To be published.

5. The term enforced is used to distinguish the hydrophobic bonding of the reactants in the activated complex from hydrophobic interactions not dictated by the activation process, which may lead to complexes of different geometry.

6. (a) Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (b) Blake, J.F.; Lim, D.; Jorgensen, W.L. *J. Org. Chem.* **1994**, *59*, 803.

7. Grieco, P.A. *Aldrichim. Acta* **1991**, *24*, 59 and references therein.

8. In most studies on Lewis-acid catalysis of DA reactions water-sensitive catalysts are employed, although there are Lewis acids known that remain active when small amounts of water are present. See for example: Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.

9. For recent reviews see: (a) Kagan, H.B.; Riant, O.; *Chem. Rev.* **1992**, *92*, 1007. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

10. Prepared following a modified literature procedure described in: Engler, C.; Engler, A. *Chem. Ber.* **1902**, *35*, 4061.

11. Chaberek, S.; Martell, A.E. *Organic Sequestering Agents*; Wiley: New York. 1959.

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